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Is European market access the biggest **potential prize in rare disease development?**

Orphan drugs are among the most expensive treatments available to healthcare systems.

Europe, long seen as impervious to premium pricing, represents the pharmaceutical industry's biggest opportunity.

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Intro

Orphan drugs are among the most expensive treatments available to healthcare systems worldwide.

Their substantial cost, coupled with the small patient populations they benefit, means orphan drugs are paradoxically inconsequential in the singular, yet intimidating as a category, to payers.

Thankfully, for those suffering with a rare disease, new drug development in the largest global markets - the US and Europe – is fuelled by incentives for manufacturers and continuous innovation (Figure 1).

Figure 1. *Incentives devised to promote orphan drug R&D in the US and Europe*

US - FDA	Europe - EMA
Offer orphan drug designation	Offer orphan drug designation
Early access schemes	Early access schemes
Exclusivity for up to 7 years post-approval	Exclusivity for up to 10 years post-approval
50% tax credit on R&D costs for Phase I-III clinical trials	Reduced fees for EMA protocol assistance
User fee waivers for companies with <$50 million annual revenue	Reduced fees for administrative and procedural assistance
Fast-track approval	Conditional marketing authorisation
Breakthrough Therapy designation	PRIME and subsequent Adaptive pathways approach

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The US and Europe each benefit from similar incentives to research and discovery of new drugs, and while these facilitate drug innovation, they do not impose any direct influence on pricing.

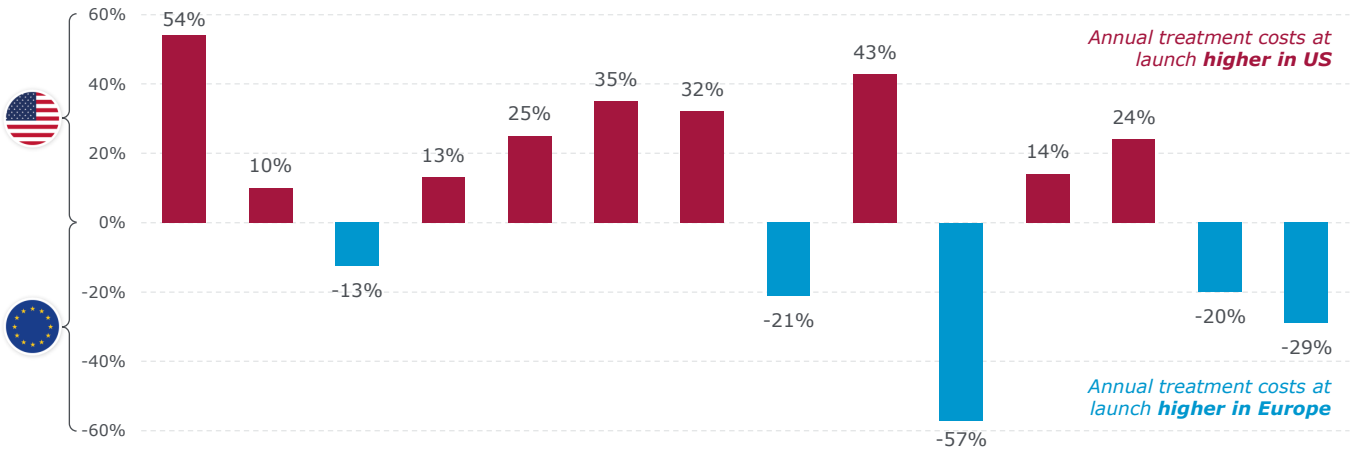
Historically, a clear price differential for pharmaceuticals is assumed between US and European markets. The disparity is systemically induced, with the US market offering an insurance-based, free-pricing environment, in stark contrast to Europe's government bodies and social health insurance structure focused on value-based assessment.

Given these systemic differences, our hypothesis assumed a disparity between the US and Europe was also present in orphan drug pricing.

To test this, we compared the prices of launched orphan drugs, collated from our existing work within industry, in the US and Europe.

Figure 2. *ISPOR orphan drug pricing chart; US vs Europe*

Difference in annual treatment cost per orphan drug between US and Europe shown as percentage difference, with orphan drugs ordered by approval date



	Alprolix®	Orkambi®	Strensiq®	Kanuma®	Ocaliva®	Spinraza®	Zejula®	Brineura®	Symkevi®	Crysvita®	Galafold®	Takhzyro®	Tegsedi®	Givlaari®
FDA approval	03/2014	07/2015	10/2015	12/2015	05/2016	12/2016	03/2017	04/2017	02/2018	04/2018	08/2018	08/2018	10/2018	11/2019
EMA approval	05/2016	11/2015	08/2015	08/2015	12/2016	05/2017	11/2017	05/2017	10/2018	02/2018	05/2016	11/2018	07/2018	03/2020

Note: *Prices for Europe are list prices and subject to confidential discounts at a national, regional and even local level. Additionally, prices in Europe are subject to periodic re-pricing, for example in Germany, Tegsedi has had a 28% discount from launch to current price, following price re-negotiation after 1-year free pricing.*

Our analysis confirms that there is an overall disparity in list price between the US and Europe, with drugs seemingly "cheaper" in the latter. However, if we isolate the drugs approved within the last four years, compared with those approved almost seven years ago, we see a different trend.

Grouping the seven orphan drugs that were earliest to market in our analysis (Alprolix® up to Zejula®), we see that **the majority (86%) are more expensive in the US than in Europe**. Grouping the later seven orphan drugs, from Brineura® up to Givlaari®, we see that **less than half (42%) are more expensive in the US than in Europe**. The prevailing trend is a minimised difference in list prices between US and EU.

Implications of this trend on pricing in the future, will be dictated not only by key drivers of commercialisation in both markets, but crucially by the sustainability of the market as a whole.

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Sustainability in drug funding

Sustainability is key, and commercialised drugs constitute just the tip of the iceberg in rare disease; it is what lies beneath that will further compound the price disparity between the US and Europe.

The tip itself? The **1000 currently commercialised orphan drugs** in the US, and the 500 in Europe.[1,2] And the submerged bummock? The **5,000 to 8,000 rare diseases** that currently lack specific treatment. As of 2021, **only 12.5% of the potential market** has been captured.

Given the anticipated growth within the orphan drug space, it is easy to imagine how a specific, costly product to treat each rare disease will create a huge strain on healthcare systems in the aggregate.

Manufacturers of novel orphan therapies must proactively identify and action the following to ensure success:

- The drivers of price disparity between the US and Europe
- How these drivers may change in the future
- How changes can be overcome to ensure the future successful commercialisation of many more orphan drugs

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Is a lack of understanding impacting orphan drug prices?

At FIECON, we consistently and successfully help our clients gain market access at commercially acceptable prices. On a day-to-day basis, we support our clients with market access strategy, communication tools and deliverables that inform pricing decisions.

In an effort to characterize uncertainties around the impact of key drivers of price in both the US and Europe and to understand future fears for the orphan drug market as a whole, we spoke to industry leaders at key orphan drug manufacturers. Said manufacturers had a track record of achieving commercialisation success in the US and/or Europe.

Figure 3. *Showing the key drivers listed which were tested*

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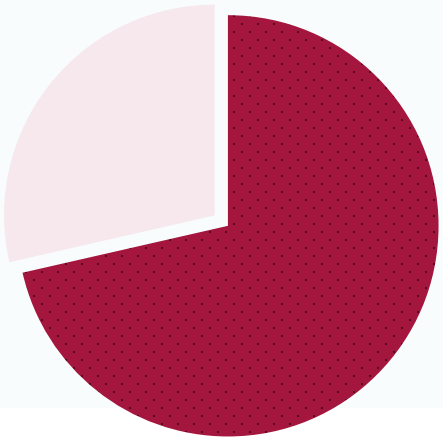
Figure 4. Industry leader split in understanding of the impact of key drivers



72%

of industry leaders do **NOT agree on the specific impact of key drivers on commercial success**

Following our discussions, it became clear that manufacturers are still grappling with the specific impact of key drivers for orphan drug commercialisation. Consensus was reached on several key issues, but there was little alignment on their potential resolution.

Market Drivers

A disconnect between problems and solutions was observed throughout our discussions. Value-based pricing formed a 'buzz' word for most discussions, but there was little clarity on the details of demonstration.

There was also a consistent narrative that higher prices were achievable in the US compared to Europe. However, upon further discussion this was largely a remnant of historical assumptions and institutional memory concerning high US vs Europe list prices, an assumption that may no longer hold true in the modern day.

Another consistent opinion was on the current importance of international reference pricing as a driver of price in orphan drugs, however industry data shows this has waned in recent years.

Geographic Drivers

When assessing from a market perspective, manufacturers shared uncertainty in achieving complete success in Europe, with government budget pressure fuelling additional evidence requirements for HTA submissions in key markets.

The requirement for successful navigation of processes, such as early access schemes and managed entry agreements, have some manufacturers feeling they lack the requisite expertise and experience when commercialising within Europe.

Navigation is further hindered by the lack of acceptance, in most key European markets, of US evidence and real world data generated through similar schemes and agreements stateside.

Manufacturers viewed this as a common issue as US access is often achieved first, before manufacturers set sail for Europe and subsequent global markets.

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Product Value Communication Drivers

Product value demonstration is a key issue, and it emerged as consensus among polled manufacturers who found:

- Difficulty in demonstrating value in their focus market (US/EU)
- Difficulty realising value in their opposing market, and
- Uncertainty and outdated views around the impact of changes implicating both markets for the future.

These pain points, chiefly the inability to optimally demonstrate value, have slipped under the market radar because the issue is subjective (versus objective geographic or market conditions).

Gaining certainty around the impact of changes to come, and how to tackle them with value arguments that are compelling to local payers, clearly emerged as a must for orphan drug manufacturers.

3 Changes to commercialisation

Facilitating access to orphan drugs has been an explicit goal of government bodies and regulators throughout the US and Europe. Manufacturers unaware of the latest policies may end up missing out on considerable allocated budget, or spend more money during commercialisation than is necessary.

Nuanced requirements exist for orphan drugs seeking reimbursement across all global markets and there are several evolving policies that may impact future access and reimbursement should they be enacted as law.

Outlined below are the key changes in policy in orphan therapy, highlighting not only future pain points for manufacturers during commercialisation, but also potential improvements to processes which manufacturers may take advantage of, particularly with respect to the newly fenced budgets for orphan drugs in key European markets.

In the US

Potential price reform proposals

Price reforms have been intensely debated among the chambers of congress for years, however, they have never quite tipped over the edge into enacted policies.

Today, there remains two regulations from the Trump-era, as well as two newer policies favoured following the Biden administration, which are on the docket for congressional debate and vote.

Price reform proposals in the US have not taken direct aim at orphan drugs, though their impact could disproportionately effect pricing in the area in the years to come.

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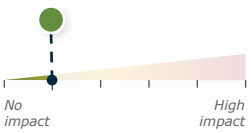
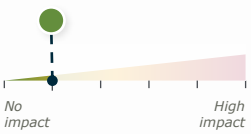
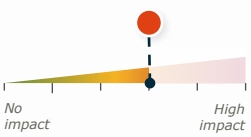
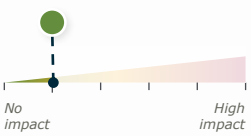
Price reform proposal[3]	Impact on orphan drug pricing	Reason
Favoured nation model - currently frozen under court order, this bill looked at utilising international reference pricing to inform drug prices within the US. However, the current model structure is flawed and unlikely to be unfrozen, with suggestions to modify the bill to tie in drug price with effectiveness by a third-party (e.g. the Institute of Clinical and Economic Review (ICER)), much like the value-based assessment seen within the EU.		Unlikely to ever be passed in the capacity that international reference pricing would dictate the price of an orphan drug within a free market like the US.
ICER - the ICER utilise a value-base framework to independently assess the clinical and cost-effectiveness of select treatments approved by the FDA. Manufacturers have not benefited greatly thus far from ICER's reports on new orphan drugs entering the market, who report the high list prices as not being cost-effective. However, ICER's assessment lacks validity compared to value-based assessments conducted across most of Europe. A lack of validity, compared to assessment in Europe, is down to ICER's disregard of physician, patient or societal inputs to inform cost-effectiveness, all of which are regarded as key factors when assessing an orphan product.		ICER typically have targeted disease areas where there is already a lot of spending. Realistically, the orphan drug market is unlikely to become one of those markets in the near future, until significant inroads are made into their development and the orphan market becomes a large collective cost.
Rebate rule – currently delayed until January 2023, the rebate rule stipulates that any savings made from rebates should be realised by the consumer at the point of sale, instead of going directly to the health insurer or PBM.		Rebate rules are typically designed to improve affordability for drugs with a low price tag that are commonly prescribed within the population. Orphan drugs are typically priced at $100,000 and above, meaning that although rebates would be due, the savings made would not detract from the substantial initial investment required.
Drug-price reforms – The Biden administration is likely to test reform components being currently considered by Congress. One key component is around inflation rebates for increased prices, something that would cause orphan drug prices within the US to increase further.		Typically, drug-price reforms target existing therapies on the market that have received an un-just initial price compared to the market on the whole. Orphan drugs achieve such a high list-price, that this is unlikely. However, with more scrupulous rebating and with an aggressive pricing strategy, orphan drug manufacturers could see value in utilising this reform for orphan products that find themselves within a market with more than one therapy available.
Outcomes-based contracting – Medicaid (the US national public health insurance program) has announced that it is looking into tackling the high cost of cell/gene therapies through potential outcomes-based contracts with manufacturers, much like the innovative pricing agreements seen in Europe. Similarly, some US states have arranged full-service packages with manufacturers, including outreach, testing and the drugs themselves for a specific, prevalent disease, at a fixed price.		Outcomes-based contracting has always been stuck in a 'legal limbo'. Manufacturers do not ineligible patients to receive their drug and eligible patients also need to be ratified by insurers prior to receiving treatment. For orphan indications, this baseline risk needs to be monitored even tighter, so it is not likely that any outcomes-based contracting will involve orphan products for now.

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Congressional review of the above proposals and amendments have been halted over the past year or so because of COVID-19. Now, committees are fleshing out the above ideas for presentation and debate within Congress. Manufacturers must be aware of when policy proposals or amendments are ratified by Congress and signed into law, in order to maintain profitable access with payers in the US and ensure optimal gross to net spreads on price for key therapies.

Today in the US the general lack of therapies currently available for most orphan conditions, coupled with the low net budget impact of payer adoption, means that high gross prices will remain unchecked and little pressure will be applied on net pricing. This trend is particularly strong among first-in-class therapies for previously untreated orphan indications, but must be caveated by the fact that only list prices are taken into account, with rebate negotiations unknown in the majority of cases.

In Europe

Government budget pressure

Centralised, value-based assessment of drugs in each European market makes restrictions enforceable from a macro to micro scale[4]. Each market has a different view of "value" and a nuanced approval process dictated by government budget pressure.

Since the financial crash in 2008, governments and other purchasers enhanced their bargaining power to negotiate lower drug prices, through strengthened policies, allowing national funding for healthcare not to falter in the wake of diminished GPD. Those strengthened policies, strained by the pressure of COVID-19, consist of; centralised procurement, price reductions, price-volume and budget impact agreements, external and internal reference pricing, tendering and distribution margins. These are what manufacturers feel now, when negotiating high prices for their drugs.[4,5]

Cost-effectiveness analysis

In more recent years, Europe has ushered in adaptations to submission requirements in some key European markets. Namely the introduction of cost-effectiveness analysis - a requirement in Italy, and also in some HTA submissions within Spain, with recommendation for full-time inclusion nationally following the GENESIS guidelines.

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BeNeLuxA Initiative

In addition to strengthened policies nationally, initiatives to streamline HTA assessment and ease government budget pressures have incentivised collaboration across nations, through joint HTA assessments, joint price negotiations, and in some cases joint purchasing blocks. Between Belgium, the Netherlands, Luxembourg, Ireland and Austria, the creation of the BeNeLuxA Initiative was prompted due to the exact submerged iceberg we have identified, that is the anticipated rapid growth in the number of new orphan drugs being produced.

This initiative, like most other cross-border market access collaborations in Europe, aims to promote horizon scanning for future drugs and spending, information, HTA and policy sharing, and joint pricing negotiations to improve bargaining power with manufacturers.[6] Most recently, the initiative collaborated to agree a joint price for SMA treatment Zolgensma, via Health Technology Assessment's (HTA) in Belgium, Ireland and the Netherlands, with Austria acting as an external reviewer.[7]

EUNetHTA Joint Actions

Similarly, the European Commission put forward a proposal for a joint clinical assessment (JCA) that has now been extended to September 2023.[8] The EUnetHTA 21 will build on the success of the EUNetHTA Joint Actions, covering JCA and scientific consultation (JSC) for manufacturers developing orphan drugs.[9]

EUNetHTA builds efficiencies with health technology assessors during the processing, analysis and interpretation of data, with a primary focus on solving methodological challenges encountered by HTA bodies. Although not always completely effective (due to misalignment on national regulations, lack of resources and lack of methodological clarity in some cases), for manufacturers, there is potential for faster and less resource intensive national assessments with a predictable and consistent process that can be transferred between key European markets (excluding the UK). Additionally, manufacturers benefit from an improvement in EMA cooperation, alongside predictable spending, and process plans.

Innovative Medicines Fund (IMF),

Currently, government budget pressure for orphan products in most European markets is not substantial.

With developments in gene therapy likely expediting their production in the near future, key European markets are making the necessary preparations to support the requisite investment and uptake. This is no more so true than in the UK, with NICE's announcement of the Innovative Medicines Fund, acting as a £340m pot to aid reimbursement decisions for promising therapies in burdensome therapy areas.[10]

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Innovation in key European markets has improved horizon scanning, HTA process and, in some cases, has led to specific funds for orphan drugs, should the right one come along. It seems that individual national changes to market access in Europe have allowed innovation to be tested on a smaller scale and then adopted throughout most of Europe, bar a few exceptions – e.g., Germany's social health insurance system or Spain's reimbursement price cap. This is in stark contrast to the lack of 'big picture changes' to price reforms within the US, a possible contributing factor to the recent trend in higher orphan drug prices achieved within Europe.

Strengthened policies, joint initiatives and innovation outline the gauntlet for orphan drug manufacturers within Europe. Although successful negotiation of market specific HTA processes is a complex task, achieving access to national budgets within the last four years has been, and should continue to be, worth the duel.

4 What does it mean for Manufacturers?

For manufacturers developing orphan drugs, there is no denying the attractiveness of the market. The iceberg of orphan indications without targeted therapy is an exciting prospect for manufacturers looking to save the lives of patients with the most severe and debilitating of diseases. Coupled with the recent trend towards higher prices achieved in Europe, there is even more reason for global manufacturers to identify, assess, and action market drivers to achieve patient access at commercially attractive prices.

However, if manufacturers have an antiquated understanding of the key drivers, future changes and innovation on the horizon in both the US and Europe, they can expect a reduced yield in net profit over both markets combined.

Europe is a key region that manufacturers need to gain access to, to achieve viable prices to bolster yield and sustain global business. Key opportunities to capitalise on:

- ✓ Changes to HTA submission requirements
  (e.g. increased use of cost-effectiveness studies across Europe)
- ✓ Joint purchasing initiatives and market specific innovation
- ✓ Allocated orphan drug budgets

These recent amendments to market access within Europe are enticing for launch and improving patient access. However, their procurement requires compelling value communication, underpinned by a clear narrative and robust evidence.

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The European Opportunity

For a manufacturer to execute on the European opportunity, out-licensing may seem a logical choice in the short-term. Out-licensing requires identification of a reliable European partner, negating the need to tackle change or innovation, nor waste resource on per-market HTA nuances to achieve access.

However, for long-term development with a global view, manufacturers that launch themselves and refrain from out-licensing into Europe, have the ability to realise tremendous value creation. This value is reflected in equity, but also in infrastructure, vendor relationships and a salesforce, which can spring-board a multitude of strategies in the future, including pipeline drug launch in Europe for the litany of conditions still lacking therapy.

In addition to this, the targeted nature of orphan conditions means the salesforce investment is targeted specifically to 'national expert' physicians, who treat the majority of cases of each rare disease in each nation. A smaller investment to reach scale is required, which is an exciting opportunity for all manufacturers attempting to achieve commercial success for the first time in Europe.

As we've discovered from our work successfully commercialising 25+ orphan drugs for pharmaceutical companies globally, achieving success during launch lies squarely in demonstrating value through rigorous and tailored evidence.

Understanding the nuanced HTA requirements in Europe and profitable access pathways is only the first step; the practical applications in each market, targeting the relevant customers, is where success or failure is determined.

Critically, developing a successful evidence package requires manufacturers to gather and maintain an in-depth market knowledge for each key market from clinical, economic and humanistic perspectives. If this can be achieved by manufacturers, either individually or with specialist support, we will continue to witness the growth of the orphan drug market, as a dynamic area of innovation serving patient needs, and a highly profitable avenue for firms discovering and marketing therapies worldwide.

FIECON have supported the commercialisation of 25+ orphan drugs globally

100%
HTA success rate

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